The Incidence of Kaposi Sarcoma Among Injection Drug Users With AIDS in the United States

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Summary: Some studies report increased prevalence of human herpesvirus 8 (HHV-8), the causative agent of Kaposi sarcoma (KS), among injection drug users (IDUs), suggesting that HHV-8 may be transmitted through blood-borne or other exposures common in this population. Since an elevated HHV-8 prevalence in IDUs would likely lead to increased KS incidence, KS incidence was studied in IDUs and non-IDU's with AIDS. AIDS-related KS cases were identified using linked US AIDS and cancer registry data for 25,891 women, 47,782 heterosexual men, and 90,616 men who have sex with men (MSM). KS arose in 7099 persons with AIDS. KS incidence was highest for MSM (5.7 per 100 person-years), substantially lower for heterosexual men (0.7 per 100 person-years), and lowest for women (0.4 per 100 person-years). After adjustment for age, race, registry location, and year of AIDS onset, relative risks for KS associated with injection drug use were 1.3 (95% CI, 0.9–1.8) among women, 1.1 (0.7–1.6) among heterosexual men, and 0.9 (0.8–0.9) among MSM. It is concluded that injection drug use was not associated with an increased risk of AIDS-related KS. Thus, these data suggest that IDUs' risk of acquiring HHV-8, through needle sharing or other behaviors related to injection drug use, is low.

Key Words: Kaposi sarcoma, human herpesvirus 8 (Kaposi sarcoma–associated herpesvirus), AIDS, cancer, epidemiology, injection drug use

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Kaposi sarcoma (KS) is the most common AIDS-associated neoplasm in the United States.[1] The pathogenesis of KS is not fully defined but human herpesvirus 8 (HHV-8, also known as KS-associated herpesvirus) is known to play a causal role.[2] HHV-8 infection precedes KS, and among persons with HIV/AIDS the prevalence of HHV-8 antibodies is a strong predictor of KS risk.[3,4] The high incidence of AIDS-associated KS among men who have sex with men (MSM)[5–8] and high seroprevalence of HHV-8 in this group[3,9,10] suggest that the primary mode of transmission of HHV-8 in the United States is through sexual contact among men. Additionally, blood-borne exposures are being investigated as another mode of HHV-8 transmission. Recent evidence suggests that individuals who use injection drugs (IDUs), especially over a prolonged period, are at higher risk for HHV-8 infection than those who do not, even after consideration of gender or sexual orientation.[11–13]

Few data are available on KS risk among IDUs. In the present study, we used data from a large US registry-based cohort of individuals with AIDS to compare the incidence of AIDS-associated KS in IDUs to that in non-IDUs. We reasoned that an increased incidence of KS among IDUs would likely reflect a relatively high prevalence of HHV-8 and would suggest that needle sharing or other behaviors common in IDUs contributes to HHV-8 transmission.

METHODS

The AIDS Cancer Match Registry study linked US AIDS and cancer registries from 6 states and 5 metropolitan areas to identify cancers arising in individuals with HIV infection or AIDS.[14] The study includes data on 197,641 individuals in whom AIDS was diagnosed at 18 years of age or older between 1980 and 1996, the era prior to the introduction of highly active antiretroviral therapy (HAART). In the present analysis, data from Florida were excluded (n = 33,352 individuals) because of inconsistent coding of KS diagnoses in the early years of the study. Thus, 164,289 individuals in whom AIDS had been diagnosed were studied.

IDU was identified based on categories of HIV/AIDS exposure reported to AIDS registries. AIDS registry data were also used to categorize subjects into 3 groups according to gender and sexual orientation: women, MSM, and heterosexual men (ie, other men). Cases of KS arising in these subjects 4–27 months after AIDS onset were identified through diagnoses recorded in the cancer registry only (n = 3335, 47%), the AIDS registry only (n = 1323, 19%), or both (n = 2441, 34%). When both registries reported KS for the same individual, the earliest date of diagnosis in either registry was used in analyses. Individuals who developed KS 0–3 months after AIDS onset were excluded from analysis (ie, not counted at risk or

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as KS events) to reduce potential ascertainment bias at the time of initial AIDS evaluation. We suspected that ascertainment bias in this early post-AIDS period could arise because KS is itself an AIDS-defining illness, and because the risk for other AIDS-defining illnesses, which might occur earlier in the course of HIV infection and accelerate the onset of AIDS, could differ for IDUs and non-IDUs.

KS incidence was calculated as the number of KS cases divided by the number of person-years at risk. Time at risk began 4 months after AIDS onset and ended at the earliest of KS diagnosis, 27 months after AIDS onset, or loss to follow-up. Analyses were stratified according to gender and sexual orientation, since these groups have different risks of acquiring HHV-8 infection sexually.[9,10,12] Poisson regression was used to compare KS incidence between IDUs and non-IDUs within each stratum, test for differences in KS incidence across demographic categories, and adjust for potential confounding in multivariate analyses. CD4 counts, routinely available only since 1990, were those closest to the time of AIDS onset.

RESULTS

The study group comprised 25,891 women, 47,782 heterosexual men, and 90,616 MSM (Table 1). The majority of women (61%) and heterosexual men (93%) used injection drugs, whereas only 10% of MSM used injection drugs. On average, women were slightly younger at AIDS onset than heterosexual men and MSM (mean ages of 35.6 vs. 38.4 and 37.4 years, respectively). Approximately half of the women and heterosexual men were African American whereas the majority of MSM (62%) were white. The composition of the 3 groups also differed geographically. More than 70% of women and heterosexual men were diagnosed with AIDS in New Jersey or New York, whereas <8% came from California sites (Los Angeles, San Diego, San Francisco). In comparison, 42% of MSM with AIDS were from California sites. For all 3 groups, the majority of subjects developed AIDS in 1991–1995. CD4 counts at AIDS onset, when known, were similar in all groups (Table 1).

Among persons with AIDS, 7099 developed KS. By strata, KS incidence after AIDS onset was highest among MSM (5.7 per 100 person-years), substantially lower among heterosexual men (0.7 per 100 person-years), and lowest among women (0.4 per 100 person-years). Within each gender/sexual orientation stratum, KS incidence was not higher in IDUs than non-IDUs (Table 2). Among MSM but not other groups, KS incidence was significantly lower among IDUs than non-IDUs (4.7 vs. 5.8 per 100 person-years, $P < 0.001$). The peak incidence in all groups was highest in young adults, falling most noticeably with age among MSM. Among heterosexual men and MSM, KS incidence was lower in African Americans than in other racial/ethnic groups. In all 3 strata, KS incidence was higher among individuals diagnosed with AIDS in California registries than elsewhere. In addition, KS incidence decreased significantly with calendar year in every stratum, although the decline was statistically significant only among MSM (from 10.2 per 100 person-years in 1981–1985 to 4.9 per 100 person-years in 1991–1996). In all strata, KS incidence increased significantly as CD4 count declined (Table 2).

In a multivariate analysis, we examined the association between IDU and KS incidence adjusting for potential confounding by age, race, year of AIDS onset, and registry site. After multivariate adjustment, KS incidence did not differ between IDUs and non-IDUs among women (adjusted relative risk, 1.3; 95% CI, 0.9–1.8) or heterosexual men (1.1, 0.7–1.6). Among MSM, adjustment for these factors reduced but did not eliminate the lower risk for KS among IDUs compared with non-IDUs (adjusted relative risk, 0.9; 95% CI, 0.8–0.9). Further adjustment for CD4 count at AIDS onset for the 36% of subjects with available CD4 count data (Table 1) resulted in little change of relative risks. The CD4 adjusted relative risks were 1.2 (95% CI, 0.7–2.3) for women, 1.8 (95% CI, 0.9–3.2) for heterosexual men, and 0.9 (95% CI, 0.8–1.0) for MSM.

DISCUSSION

Among individuals with AIDS in the United States, KS incidence was highest among MSM, intermediate among heterosexual men, and lowest among women, consistent with results from prior studies.[5,8] Importantly, after stratifying on gender and sexual orientation, we found that IDU was not associated with an increased incidence of KS. Our finding that KS incidence was unrelated to IDU remained unchanged after adjustments for demographic factors and CD4 counts. These results regarding KS incidence among individuals with established AIDS agree with those of Beral et al,[5] who reported that, among individuals with new-onset AIDS, the proportion of individuals presenting with a diagnosis of KS was similar for IDUs and non-IDUs.

These observations suggest that HHV-8, the causative agent of KS, is not transmitted efficiently enough, through needle sharing or other behaviors among IDUs, to significantly affect KS rates. Prior studies of IDUs have yielded inconsistent results regarding possible HHV-8 transmission through needle sharing. One of the first US studies to report a significant positive association between HHV-8 infection and IDU was a cross-sectional multicenter study of women with or at risk for HIV infection.[12] The study found increased HHV-8 seroprevalence with frequent or intensive injection drug use. Similarly, another study of men and women IDUs in San Francisco found that HHV-8 seroprevalence increased with duration of drug use after controlling for sexual behavior.[11] A third US study of HHV-8 among pregnant HIV-infected women observed elevated HHV-8 seroprevalence in those who reported IDU or were infected with hepatitis C virus, a blood-borne pathogen.[13]

TABLE 1. Characteristics of Study Subjects

Characteristic	Women (n = 25,891)	Heterosexual Men (n = 47,782)	MSM (n = 90,616)	*P* Value
Injection drug use				<0.001
Yes	15825 (61)	44213 (93)	9296 (10)	
No	10066 (39)	3569 (7)	81320 (90)	
Age at AIDS diagnosis, y				<0.001
18–29	5696 (22)	5036 (11)	16376 (18)	
30–39	13259 (51)	23536 (49)	42337 (47)	
40–49	5489 (21)	15439 (32)	23190 (26)	
50–59	1116 (4)	3134 (7)	6906 (8)	
60+	331 (1)	637 (1)	1807 (2)	
Mean ± SD	35.6 ± 8.1	38.4 ± 7.7	37.4 ± 8.8	
Race/ethnicity				<0.001
White	5797 (22)	9977 (21)	56455 (62)	
African American	13601 (53)	23687 (50)	19094 (21)	
Hispanic	6336 (24)	13897 (29)	13522 (15)	
Other	157 (1)	221 (<1)	1545 (2)	
Registry				<0.001
Atlanta	1101 (4)	1951 (4)	6058 (7)	
Connecticut	1426 (6)	2729 (6)	1929 (2)	
Illinois	1468 (6)	2811 (6)	7623 (8)	
Los Angeles	1134 (4)	1512 (3)	19585 (22)	
Massachusetts	1460 (6)	2630 (6)	4087 (5)	
New Jersey	6051 (23)	10278 (22)	6016 (7)	
New York	12310 (48)	24457 (51)	23084 (25)	
San Diego	309 (1)	355 (1)	4597 (5)	
San Francisco	492 (2)	851 (2)	14052 (16)	
Seattle	140 (1)	208 (<1)	3585 (4)	
Year of AIDS onset				<0.001
1980–1985	616 (2)	1828 (4)	4947 (5)	
1986–1990	6852 (26)	14782 (31)	33595 (37)	
1991–1996	18423 (71)	31172 (65)	52074 (57)	
Mean ± SD	1991.5 ± 2.5	1991.1 ± 2.7	1990.6 ± 2.9	
CD4 count at AIDS onset, cells/mm^3*				<0.001
0–24	2621 (30)	4910 (34)	9253 (25)	
25–49	961 (11)	1652 (11)	4689 (13)	
50–99	1340 (15)	2194 (15)	6386 (18)	
100–149	1245 (14)	1801 (12)	5398 (15)	
150–199	1573 (18)	2199 (15)	6081 (17)	
200+	1109 (13)	1661 (12)	4694 (13)	
Mean ± SD	112.5 ± 134.6	101.9 ± 130.6	109.1 ± 116.3	

Values in table are number of subjects (%), unless otherwise stated.

*Few subjects diagnosed with AIDS before 1990 had CD4 counts available. Data on CD4 counts are thus presented for the 59,767 subjects diagnosed with AIDS beginning in 1990 and for whom CD4 counts were available (36% of all subjects included in the study).

However, another cross-sectional study of high-risk women from several major US cities did not find a significant association between HHV-8 seroprevalence and frequency of drug injection.[15] Further, an inverse relationship between daily injection use and HHV-8 seroprevalence was noted among HIV-infected IDUs in Baltimore.[16] Among MSM, studies in Seattle and San Francisco reported conflicting results regarding the association between IDU and HHV-8 serostatus.[3,17] The

TABLE 2. KS Incidence, by Gender and Sexual Orientation

Characteristics	Women			Heterosexual Men			MSM		
	KS*	RR (95% CI)	*P* Value	KS*	RR (95% CI)	*P* Value	KS*	RR (95% CI)	*P* Value
Total	0.4	—	—	0.7	—	—	5.7	—	—
Injection drug use			0.38			0.62			<0.001
Yes	0.4	1.2 (0.8–1.7)		0.7	1.1 (0.8–1.6)		4.7	0.8 (0.7–0.9)	
No	0.4	1.0		0.6	1.0		5.8	1.0	
Age at AIDS diagnosis, y			0.39			0.03			<0.001
18–29	0.5	1.0		0.8	1.0		5.0	1.0	
30–39	0.4	0.8 (0.5–1.1)		0.7	0.9 (0.7–1.2)		6.3	1.3 (1.2–1.3)	
40–49	0.4	0.9 (0.5–1.4)		0.5	0.7 (0.5–0.9)		5.6	1.1 (1.0–1.2)	
50–59	0.2	0.3 (0.1–1.4)		0.8	1.0 (0.6–1.5)		4.7	0.9 (0.8–1.1)	
60+	0.3	0.6 (0.1–4.1)		0.4	0.5 (0.2–1.7)		2.9	0.6 (0.4–0.8)	
Race/ethnicity			0.97			0.004			<0.001
White	0.4	1.0		0.9	1.0		6.5	1.0	
African American	0.4	1.0 (0.7–1.6)		0.6	0.6 (0.5–0.8)		3.1	0.5 (0.4–0.5)	
Hispanic	0.4	1.1 (0.7–1.8)		0.7	0.7 (0.6–0.9)		6.1	0.9 (0.9–1.0)	
Other	0.4	1.1 (0.2–8.4)		0.7	0.8 (0.2–3.1)		6.5	1.0 (0.8–1.2)	
Registry			0.001			<0.001			<0.001
Atlanta	0.2	0.5 (0.2–1.6)		0.5	0.7 (0.4–1.3)		3.7	0.8 (0.7–0.9)	
Connecticut	0.3	0.7 (0.3–1.6)		0.6	0.8 (0.5–1.3)		3.8	0.8 (0.7–1.0)	
Illinois	0.3	0.7 (0.3–1.6)		0.4	0.6 (0.3–1.0)		2.0	0.4 (0.4–0.5)	
Los Angeles	1.1	2.4 (1.4–4.1)		2.1	3.1 (2.2–4.3)		6.5	1.4 (1.3–1.5)	
Massachusetts	0.1	0.3 (0.1–1.1)		0.5	0.7 (0.4–1.2)		5.2	1.1 (1.0–1.3)	
New Jersey	0.2	0.5 (0.3–0.9)		0.5	0.8 (0.6–1.0)		3.9	0.8 (0.7–0.9)	
New York	0.4	1.0		0.7	1.0		4.6	1.0	
San Diego	0.7	1.7 (0.5–5.3)		1.4	2.0 (0.9–4.6)		6.5	1.4 (1.2–1.6)	
San Francisco	0.7	1.7 (0.7–4.1)		2.1	3.0 (2.0–4.6)		10.3	2.2 (2.1–2.4)	
Seattle	0.5	1.1 (0.2–7.8)		1.0	1.5 (0.5–4.8)		5.8	1.2 (1.1–1.4)	
Year of AIDS onset			0.17†			0.34†			<0.001†
1981–1985	0.6	1.0		0.9	1.0		10.2	1.0	
1986–1990	0.5	0.8 (0.3–2.2)		0.7	0.8 (0.5–1.3)		6.4	0.6 (0.6–0.7)	
1991–1996	0.4	0.6 (0.2–1.7)		0.7	0.7 (0.5–1.2)		4.9	0.5 (0.4–0.5)	
CD4 count at AIDS onset cells/mm^3‡			0.02†			<0.001†			<0.001†
0–24	0.7	3.5 (1.2–10.1)		0.9	2.2 (1.1–4.5)		7.8	4.2 (3.5–5.1)	
25–49	0.6	3.4 (1.0–11.2)		1.1	2.7 (1.3–5.9)		7.3	3.9 (3.2–4.8)	
50–99	0.4	2.1 (0.6–7.2)		0.6	1.5 (0.7–3.4)		6.2	3.3 (2.7–4.0)	
100–149	0.2	1.1 (0.2–4.2)		0.5	1.1 (0.5–2.7)		4.3	2.3 (1.9–2.8)	
150–199	0.2	1.0		0.3	0.8 (0.3–2.1)		2.7	1.5 (1.2–1.8)	
200+	0	—		0.4	1.0		1.9	1.0	

*Incidence of KS, per 100 person-years.
†Test for trend.
‡Data on incidence are presented for the 59,767 subjects diagnosed with AIDS beginning in 1990 and for whom CD4 counts were available (36% of all subjects included in the study).
RR, relative risk.

only longitudinal study to examine the relationship between IDU and HHV-8 was conducted in Amsterdam.[18] In that study, the overall seroconversion rate for HHV-8 was low, and due to the small number of seroconversions, risk factors for HHV-8 seroconversion were not examined. However, HHV-8 seroprevalence was not increased among IDUs. In other European studies, heightened HHV-8 seroprevalence was observed in IDUs in Spain[19] and Rome[20] but not Sicily.[21]

The variation in results across seroprevalence studies suggests that if injection drug use can transmit HHV-8 infection, the magnitude of the effect is somewhat small and can be observed only in individuals who injected drugs over a very long period or with great frequency.[11,12] Data on duration and frequency of drug use were not available for subjects in our registry-based cohort, and it is likely that a wide range of IDU patterns existed among our subjects. Thus, some transmission after long-term or highly frequent IDU cannot be ruled out, although our negative findings suggest that the overall risk of HHV-8 transmission through needle sharing is low. Along these lines, a recent study of Ugandan children with sickle cell disease estimated the risk of HHV-8 transmission through blood transfusion to be 6% per infected unit.[22] Given this low risk of transmission through exposure to much larger amounts of fresh blood, the risk per needle exposure would be very low indeed.

Other social factors may have affected KS incidence in our study population. For unknown reasons, cigarette smoking has been associated with a reduced risk of AIDS-related KS in the United States[6,7] and classic KS in Italy.[23] Although IDUs smoke more than the general population,[24] it is unclear whether, among persons with AIDS, smoking prevalence differs between IDUs and non-IDUs. Information on tobacco use was not available in our registry database. However, IDUs in our study did not have a higher incidence of lung cancer than non-IDUs (data not shown), suggesting that smoking differences between IDUs and non-IDUs were not so large as to obscure an increased incidence of KS among IDUs.

The lack of information about sexual behavior is a limitation of our study. Exposure to HHV-8 through sexual contact among IDUs could be reduced if IDUs engage in less frequent sexual activity than non-IDUs. However, the incidence of sexually transmitted infections such as gonorrhea is reported to be higher among HIV-infected individuals who use illicit drugs than in those who do not.[25] In addition, long-term IDU is associated with an increased likelihood of trading sex for money or drugs.[26] Because we lacked data on sexual behaviors, we could not examine how differences in behaviors across groups affected our comparison of KS incidence.

It should also be noted that our study does not include data from the more recent HAART era. KS incidence has dramatically declined since the introduction of HAART in the early 1990s. The lack of data about the use of HAART in this study limits our ability to make conclusions about KS incidence rates among person with AIDS in the United States over the past 7 years. However, data from the pre-HAART era were ideally suited for inferences regarding patterns in KS incidence that could be attributed to differences in HHV-8 prevalence.

In conclusion, we found that IDU was not associated with an increased incidence of AIDS-related KS. Whether the lack of association is related to HHV-8 prevalence or other characteristics of IDUs and non-IDUs is not clear. Further studies of HHV-8 transmission and KS risk factors among IDUs are warranted.

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